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Letter to the Editor Response

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Response to Letter to the Editor from Rosenfield: "Glucocorticoid Resistance in Premature Adrenarche and PCOS: From Childhood to Adulthood"

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Abbreviations: F-Dex, fluorescein-labeled dexamethasone; GC, glucocorticoid; GCR, glucocorticoid receptor; PCOS, polycystic ovary syndrome.

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The etiology of adrenarche and polycystic ovary syndrome (PCOS) is still controversial [1, 2]. They are a heterogeneous group of disorders with similar clinical presentation, but with different etiologies. Patients with glucocorticoid resistance syndrome can present with hyperandrogenism with a clinical picture of PCOS or adrenarche. The milder forms of glucocorticoid (GC) resistance are difficult to confirm by routine tests like adrenocorticotropin, corticotropin-releasing hormone stimulation tests, and even with dexamethasone suppression tests; the results of these tests can be borderline to normal without clear cut offs. Even in documented cases of a glucocorticoid receptor (GCR) mutations as described by Chrousos et al. [3], the son of a described proband with the same GCR mutation had very mild hormonal abnormalities and borderline GC resistance as documented by [^{3}H] dexamethasone binding study.

In our study [4], we have proposed that by using a novel fluorescein-labeled dexamethasone (F-Dex) mononuclear cell-binding assay, we are able to identify abnormalities in the binding of GCs to the GCR. Hence, we were able to identify patients with alterations in GC sensitivity. This in vitro assay has demonstrated that GC resistance exists in the subgroup of patients as described in our study and etiology of this resistance can be heterogenous [4].

The accuracy of the F-Dex binding assay has been demonstrated in multiple ways. A subgroup of our 10 PCOS GC-resistant patients were enrolled in the study published by Gourgari et al. [5]. The patients in that study underwent a high dose dexamethasone suppression test and on day 6 after completion of the test, the urinary free cortisol was higher in the PCOS group than in the healthy control group [5]. Therefore, we agree with the author of the letter that poor suppression of cortisol secretion after dexamethasone is a hormonal marker of GC resistance [6]. The results of the study confirmed the accuracy of our test that patients were resistant in vitro as well.

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Also, in a cohort of the PCOS and premature adrenarche GC-resistant patients, mutational analysis of the GC gene (*NR3C1*) and the genes coding for the chaperone proteins FK506 binding proteins (*FKBP4* and *FKBP5*) were performed. The analysis revealed polymorphisms in 1 or more of these genes, which were not seen in controls. In the cohort where mutation analysis was completed, the F-Dex binding assay was shown to be dose dependent. To demonstrate that if a patient had polymorphism in more than 1 gene noted, the patient was found to be more resistant (less F-Dex binding) than a patient having only 1 gene polymorphism (manuscript in preparation). This has also confirmed the accuracy of the F-Dex binding test.

The assay was also found to be accurate and reproducible when the F-Dex studies were repeated in a group of patients at different time points. This was also demonstrated in control patients.

The concentrations of F-Dex that were chosen for the assay were not meant to equate to an exact physiological dose of dexamethasone, as has been alluded to in the letter [7]. The concentration range used in the studies was established after thorough analysis of the F-Dex concentration curve to meet detection parameters of the fluorimeter. Another reason that the F-Dex concentrations do not need to equate to a physiological dose is that our data were analyzed directly in relation to F-Dex binding examined on mononuclear cells from normal heathy controls. The difference in binding between these groups can then be used to determine GC sensitivity.

In summary, we conclude that this novel F-Dex binding assay is accurate and reproducible as shown in our paper [4]. We conclude that in patients with premature adrenarche and PCOS, the F-Dex binding assay can be used as an additional tool in the more detailed characterization of this patients. We believe that further investigations will be necessary to elucidate the etiology of GC resistance in PCOS and premature adrenarche.

Additional Information

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